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<p>(54) Title: PHENYL-ALKYL IMIDAZOLES AS H₃-RECEPTOR ANTAGONISTS</p> <div style="text-align: center; margin: 20px 0;"> <p style="margin-top: 10px;">(I)</p> </div> <p>(57) Abstract</p> <p>The invention provides novel phenyl-alkyl-imidazoles of formula (I) wherein A, R¹, R², m and n are as defined in the specification, and the group —(CH₂)_n—A—R¹ is at the 3- or 4-position, together with their pharmaceutically acceptable salts. These phenyl-alkyl-imidazoles and salts have valuable pharmacological properties, especially CNS activities and activity against inflammatory disease.</p>		

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Phenyl-Alkyl Imidazoles as H₃-receptor antagonists

FIELD OF THE INVENTION

The present invention relates to phenyl-alkyl-imidazoles having valuable pharmacological properties, especially CNS activities and activity against
5 inflammatory disease. Compounds of this invention are antagonists of the H₃ receptor.

BACKGROUND OF THE INVENTION

European Patent Application No. 0 420 396 A2 (Smith Kline & French Laboratories Limited) and Howson et al., *Bioorg. & Med. Chem. Letters*, Vol. 2
10 No. 1 (1992), pp. 77-78 describe imidazole derivatives having an amidine group as H₃ agonists. Van der Groot et al. (*Eur. J. Med. Chem.* (1992) Vol. 27, pp. 511-517) describe isothioureia analogs of histamine as potent agonists or antagonists of the histamine H₃ receptor, and these isothioureia analogs of histamine overlap in part with those of the two references cited above. Clapham
15 et al. ["Ability of Histamine H₃ Receptor Antagonists to improve Cognition and to increase Acetylcholine Release *in vivo* in the Rat", British Assn. for Psychopharmacology, July 25-28 1993, reported in *J. Psychopharmacol.* (Abstr. Book), A17] describe the ability of histamine H₃ receptor antagonists to improve cognition and to increase release of acetylcholine *in vivo* in the rat. Clapham et al.
20 al. ["Ability of the selective Histamine H₃ Receptor Antagonist Thioperamide to improve Short-term Memory and Reversal Learning in the Rat", *Brit. J. Pharm. Suppl.*, 1993, 110, Abstract 65P] present results showing that thioperamide can improve short-term memory and reversal learning in the rat and implicate the involvement of H₃ receptors in the modulation of cognitive function. Yokoyama
25 et al. ["Effect of thioperamide, a histamine H₃ receptor antagonist, on electrically induced convulsions in mice", *Eur. J. Pharmacol.*, vol. 234 (1993), pp. 129-133] report how thioperamide decreased the duration of each phase of convulsion and raised the electroconvulsive threshold, and go on to suggest that these and other findings support the hypothesis that the central histaminergic system is
30 involved in the inhibition of seizures. International Patent Publication No. WO9301812-A1 (SmithKline Beecham PLC) describes the use of S-[3-(4(5)-imidazolyl)propyl]isothioureia as a histamine H₃ antagonist, especially for

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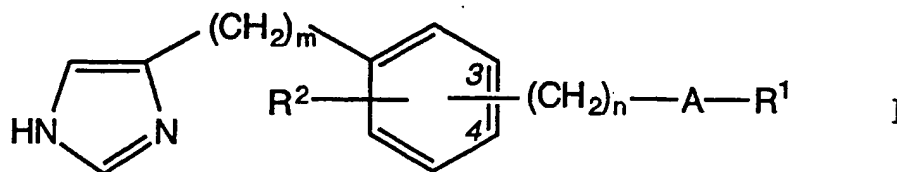
treating cognitive disorders, *e.g.* Alzheimer's disease and age-related memory impairment. Schlicker et al. ["Novel histamine H₃ receptor antagonists: affinities in an H₃ receptor binding assay and potencies in two functional H₃ receptor models"] describe a number of imidazolylalkyl compounds wherein the

5 imidazolylalkyl group is bonded to a guanidine group, an ester group or an amide group (including thioamide and urea), and compare these to thioperamide. Leurs et al. ["The histamine H₃-receptor: A target for developing new drugs", *Progr. Drug Res.* (1992) vol. 39, pp. 127-165] and Lipp et al. ["Pharmacochimistry of H₃-receptors" in *The Histamine Receptor*, eds.: Schwartz and Haas, Wiley-Liss, New York (1992), pp. 57-72] review a variety of

10 synthetic H₃ receptor antagonists, and Lipp et al. (*ibid.*) have defined the necessary structural requirements for an H₃ receptor antagonist.

SUMMARY OF THE INVENTION

The present invention provides a compound of the formula



wherein:

A is selected from $-\text{O}-\text{CO}-\text{NR}^1-$, $-\text{O}-\text{CO}-$, $-\text{NR}^1-\text{CO}-\text{NR}^1-$, $-\text{NR}^1-\text{CO}-$, $-\text{NR}^1-$, $-\text{O}-$, $-\text{CO}-\text{NR}^1-$, $-\text{CO}-\text{O}-$, and $-\text{C}(\text{:NR}^1)-\text{NR}^1-$;

20 the groups R¹, which may be the same or different when there are two or three such groups in the molecule of formula I, are selected from hydrogen, and lower alkyl, aryl, cycloalkyl, heterocyclic and heterocycl-alkyl groups, and groups of the formula $-(\text{CH}_2)_y-\text{G}$, where G is selected from CO_2R^3 , COR^3 , CONR^3R^4 , OR^3 , SR^3 , NR^3R^4 , heteroaryl and phenyl, which phenyl is optionally substituted by halogen, lower alkoxy or polyhaloloweralkyl, and y is an integer from 1 to 3;

25 R² is selected from hydrogen and halogen atoms, and alkyl, alkenyl, alkynyl and trifluoromethyl groups, and groups of the formula OR^3 , SR^3 and NR^3R^4 ;

R³ and R⁴ are independently selected from hydrogen, and lower alkyl and cycloalkyl groups, or R³ and R⁴ together with the intervening nitrogen atom can

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form a saturated ring containing 4 to 6 carbon atoms that can be substituted with one or two lower alkyl groups;

with the proviso that, when y is 1 and G is OR^3 , SR^3 or NR^3R^4 , then neither R^3 nor R^4 is hydrogen;

- 5 the group $-(CH_2)_n-A-R^1$ is at the 3- or 4-position, and the group R^2 is at any free position;

m is an integer from 1 to 3;

and n is 0 or an integer from 1 to 3;

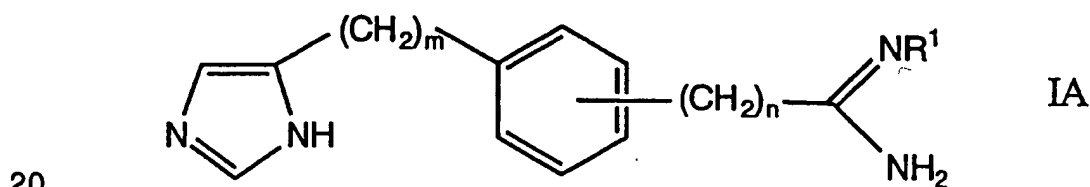
or a pharmaceutically acceptable acid addition salt thereof;

- 10 or a pharmaceutically acceptable salt thereof with a base when G is CO_2H ;

including a tautomeric form thereof.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

- Compounds of the formula I can exist in tautomeric forms by virtue of the imidazole ring: the N-hydrogen atom can tautomerize from one nitrogen atom to the other of that ring. Furthermore, compounds wherein A is a group of the
 15 formula $-C(:NH)-NR^1-$, so that the side chain is $-(CH_2)_n-C(:NH)-NR^1_2$, where only one group R^1 is hydrogen, can exist in tautomeric forms. For example, if just one group R^1 is hydrogen, then one tautomeric form can be represented by the formula



- wherein m, n and R^1 are as defined above, except that R^1 is not hydrogen. The interconversion of the tautomers is catalyzed by acids. All such tautomeric forms are covered by the invention; in particular, where a compound of formula I is referred to or a compound is named according to formula I, then all such
 25 tautomeric forms of the compound are covered.

The compounds of the invention are basic and form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic

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and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous
5 base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their corresponding salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their corresponding free base forms for purposes of this invention.

- 10 Certain compounds of the invention are zwitterionic in nature, in particular the compounds that possess a carboxyl group in G. These compounds can form pharmaceutically acceptable salts with bases also. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts, and also salts formed with pharmaceutically acceptable amines such as ammonia,
15 alkylamines, hydroxyalkylamines, N-methylglucamine and the like.

When used herein, the following terms have the given meanings:

lower alkyl (including the alkyl portions of lower alkoxy) – represents a straight or branched, saturated hydrocarbon chain having from 1 to 6 carbon atoms, preferably from 1 to 4;

- 20 lower alkenyl (in R^2) – represents a straight or branched aliphatic hydrocarbon radical having at least one carbon-to-carbon double bond (preferably in conjugation with the benzene ring that the group R^2 substitutes) and having from 2 to 6 carbon atoms;

- lower alkynyl (in R^2) – represents a straight or branched aliphatic hydrocarbon radical having at least one carbon-to-carbon triple bond (preferably in
25 conjugation with the benzene ring that the group R^2 substitutes) and having from 2 to 6 carbon atoms;

- aryl – represents a carbocyclic group having from 6 to 14 carbon atoms and having at least one benzenoid ring, with all available substitutable aromatic
30 carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted with 1 to 3 Y groups, each independently selected from halo, alkyl, hydroxy, loweralkoxy, phenoxy, amino, loweralkylamino, diloweralkylamino, and polyhaloloweralkyl. Preferred aryl groups include 1-naphthyl, 2-naphthyl and indanyl, and especially
35 phenyl and substituted phenyl;

cycloalkyl – represents a saturated carbocyclic ring having from 3 to 8 carbon atoms, preferably 5 or 6;

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halogen – represents fluorine, chlorine, bromine and iodine;

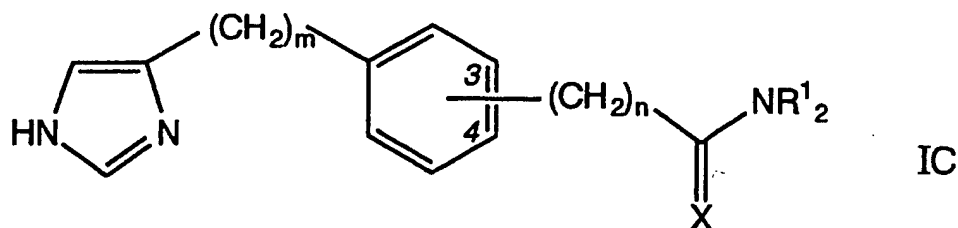
heterocyclic – represents, in addition to the heteroaryl groups defined below, saturated and unsaturated cyclic organic groups having at least one O, S and/or N atom interrupting a carbocyclic ring structure that consists of one
 5 ring or two fused rings, wherein each ring is 5-, 6- or 7-membered and may or may not have double bonds that lack delocalized pi electrons, which ring structure has from 2 to 8, preferably from 3 to 6 carbon atoms; e.g., 2- or 3-piperidiny, 2- or 3-piperaziny, 2- or 3-morpholiny, or 2- or 3-thiomorpholiny;

heteroaryl – represents a cyclic organic group having at least one O, S
 10 and/or N atom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic group having from 2 to 14, preferably 4 or 5 carbon atoms, e.g., 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2- or 4-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, or 3- or 4-pyridazinyl, etc.

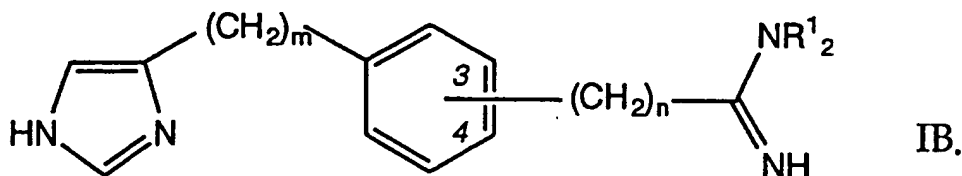
15 Preferred heteroaryl groups are 2-, 3- and 4-pyridyl;

heterocycl-alkyl – represents a heterocyclic group defined above substituting an alkyl group; e.g., 2-(3-piperidiny)-ethyl, (2-piperaziny)-methyl, 3-(2-morpholiny)-propyl, (3-thiomorpholiny)-methyl, 2-(4-pyridyl)-ethyl, (3-pyridyl)-methyl, or (2-thienyl)-methyl.

20 Preferably, A is $-\text{CH}_2-\text{NR}^1-$ or especially $-\text{C}(\text{:NH})-\text{NR}^1-$: i.e., the compounds have formula IC wherein X is H_2 or NH:



preferred compounds of the formula IC include those wherein m is 1 or 2, and n is 0, 1 or 2, more especially those of the formula



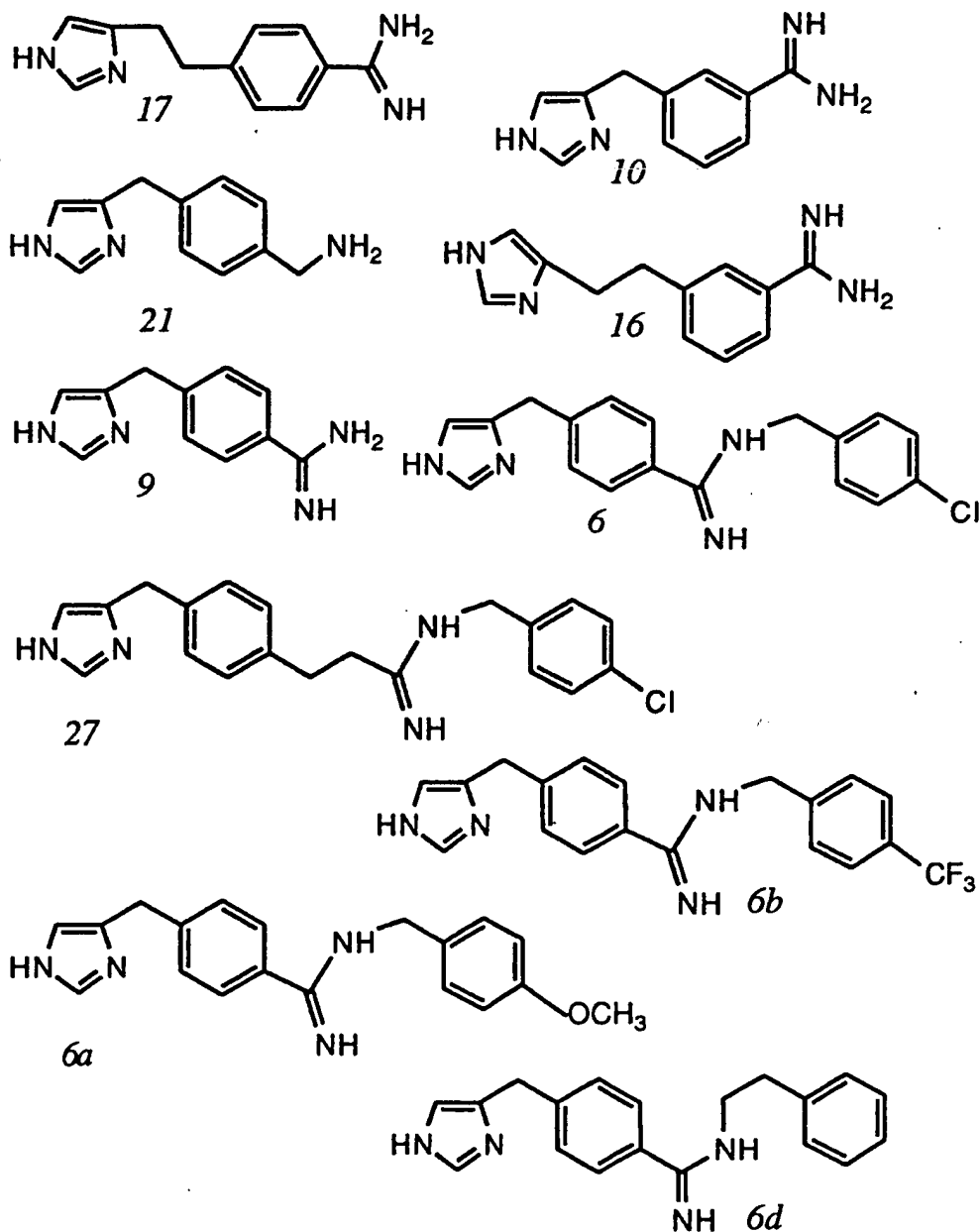
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Other preferred values of A include $-\text{O}-\text{CO}-\text{NR}^1-$, $-\text{O}-$, and $-\text{CO}-\text{O}-$. In all these compounds, the groups R^1 are as defined above, and the side chain $[-(\text{CH}_2)_n-\text{C}(=\text{X})-\text{NR}^1_2$ or $-(\text{CH}_2)_n-\text{C}(=\text{NH})-\text{NR}^1_2$] is preferably at the 4-position. In compounds of formula I and especially in compounds of formulae

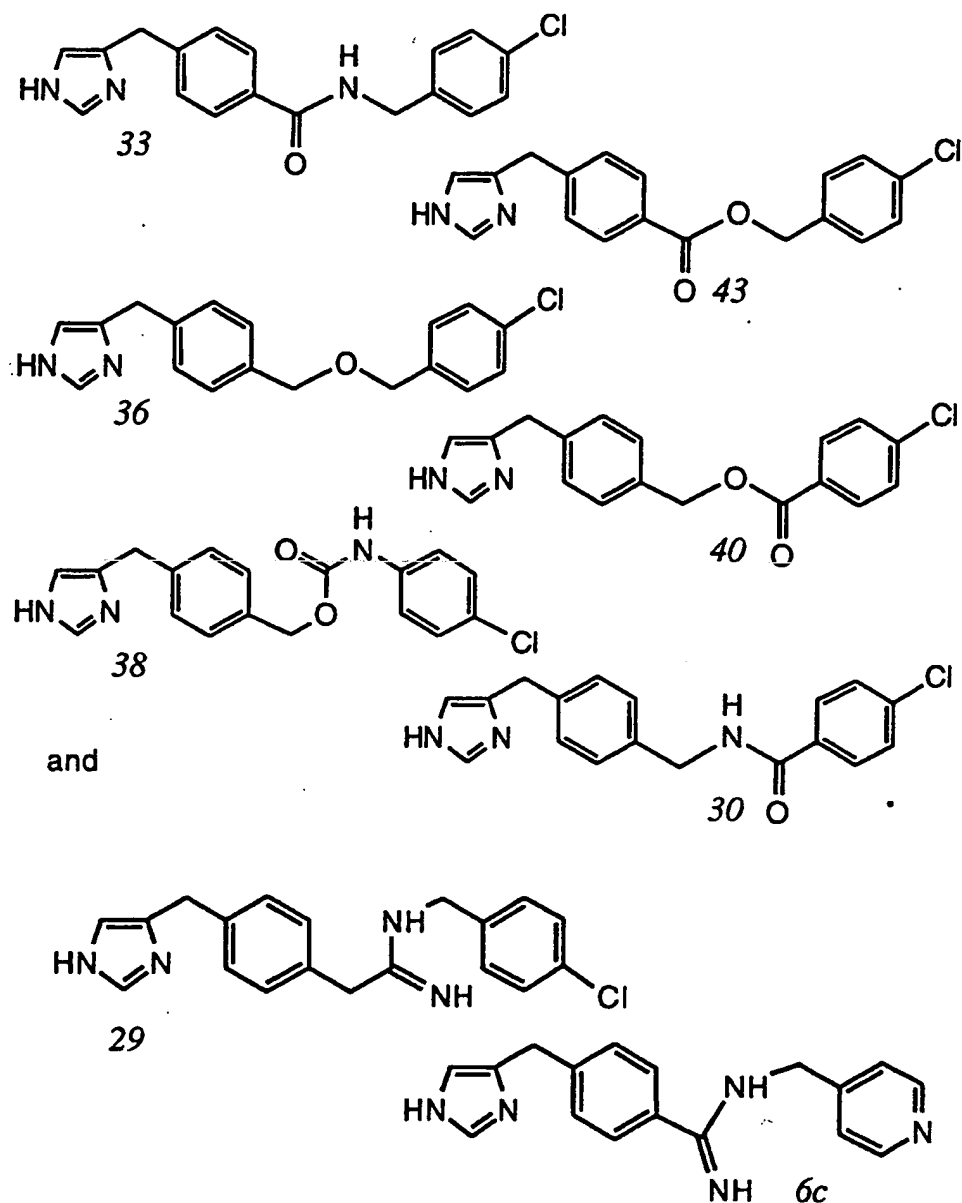
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IC and IB, one group R¹ is preferably selected from hydrogen, 2-phenylethyl, 4-chlorophenylmethyl, 4-methoxyphenylmethyl, 4-trifluoromethylphenylmethyl and 4-pyridylmethyl, but is especially 4-chlorophenylmethyl; any other group R¹ that is present is preferably a hydrogen atom or a methyl group.

- 5 Preferred compounds of the formula I include those selected from the following formulae, where the compounds bear the same numbering as in the Examples (except that the compounds in the Examples are salts, e.g., the dihydrochlorides):



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The following compounds of this invention are of special interest:

- N-[(4-chlorophenyl)methyl]-4-(1H-imidazol-4-ylmethyl)benzamide;
- 5 N-[2-(4-chlorophenyl)ethyl]-4-[2-(1H-imidazol-4-yl)ethyl]benzamide;
- N-phenylmethyl-4-(1H-imidazol-4-ylmethyl)benzamide;
- N-[(4-chlorophenyl)methyl]-3-(1H-imidazol-4-ylmethyl)benzamide;
- N-[(4-chlorophenyl)methyl]-4-[2-(1H-imidazol-4-yl)ethyl]benzamide;
- N-[2-(4-chlorophenyl)ethyl]-4-(1H-imidazol-4-ylmethyl)benzamide;
- 10 (4-chlorophenyl)methyl 4-(1H-imidazol-4-ylmethyl)benzoate;
- 2-(4-chlorophenyl)ethyl 4-[2-(1H-imidazol-4-yl)ethyl]benzoate;

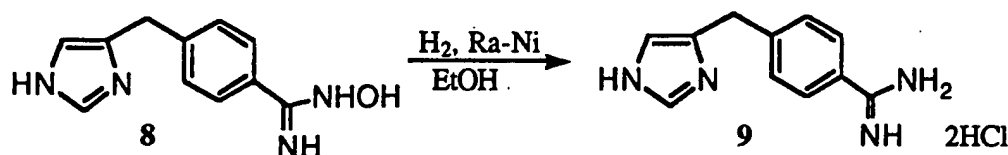
- phenylmethyl 4-(1H-imidazol-4-ylmethyl)benzoate;
(4-chlorophenyl)methyl 3-(1H-imidazol-4-ylmethyl)benzoate;
(4-chlorophenyl)methyl 4-[2-(1H-imidazol-4-yl)ethyl]benzoate;
2-(4-chlorophenyl)ethyl 4-(1H-imidazol-4-ylmethyl)benzoate;
5 4-[[4-[[[(4-chlorophenyl)methoxy]methyl]phenyl]methyl]-1H-imidazole;
4-[2-[4-[2-[(4-chlorophenyl)methoxy]ethyl]phenyl]ethyl]-1H-imidazole;
4-[[4-[(phenylmethoxy)methyl]phenyl]methyl]-1H-imidazole;
4-[[3-[[[(4-chlorophenyl)methoxy]methyl]phenyl]methyl]-1H-imidazole;
4-[2-[4-[[[(4-chlorophenyl)methoxy]methyl]phenyl]ethyl]-1H-imidazole;
10 4-[[4-[2-[(4-chlorophenyl)methoxy]ethyl]phenyl]methyl]-1H-imidazole;
[4-(1H-imidazol-4-ylmethyl)phenyl]methyl 4-chlorobenzoate;
2-[4-[2-(1H-imidazol-4-yl)ethyl]phenyl]ethyl 4-chlorobenzoate;
[4-(1H-imidazol-4-ylmethyl)phenyl]methyl benzoate;
[3-(1H-imidazol-4-ylmethyl)phenyl]methyl 4-chlorobenzoate;
15 2-[4-(1H-imidazol-4-ylmethyl)phenyl]ethyl 4-chlorobenzoate;
[4-[2-(1H-imidazol-4-yl)ethyl]phenyl]methyl 4-chlorobenzoate;
[4-(1H-imidazol-4-ylmethyl)phenyl]methyl N-(4-chlorophenyl)carbamate;
2-[4-[2-(1H-imidazol-4-yl)ethyl]phenyl]ethyl N-(4-chlorophenyl)carbamate;
[4-(1H-imidazol-4-ylmethyl)phenyl]methyl N-phenylcarbamate;
20 [3-(1H-imidazol-4-ylmethyl)phenyl]methyl N-(4-chlorophenyl)carbamate;
2-[4-(1H-imidazol-4-ylmethyl)phenyl]ethyl N-(4-chlorophenyl)carbamate;
[4-[2-(1H-imidazol-4-yl)ethyl]phenyl]methyl N-(4-chlorophenyl)carbamate;
N-[(4-chlorophenyl)methyl]-4-(1H-imidazol-4-ylmethyl)benzene-
carboximidamide;
25 N-[(4-chlorophenyl)methyl]-4-[2-(1H-imidazol-4-yl)ethyl]benzene-
ethanimidamide;
N-phenylmethyl-4-(1H-imidazol-4-ylmethyl)benzenecarboximidamide;
N-[(4-chlorophenyl)methyl]-3-(1H-imidazol-4-ylmethyl)benzene-
carboximidamide;
30 N-[(4-chlorophenyl)methyl]-4-(1H-imidazol-4-ylmethyl)benzeneethanimidamide;
N-[(4-chlorophenyl)methyl]-4-[2-(1H-imidazol-4-yl)ethyl]benzene-
carboximidamide;
4-chloro-N-[[4-(1H-imidazol-4-ylmethyl)phenyl]methyl]benzamide;
4-chloro-N-[2-[4-[2-(1H-imidazol-4-yl)ethyl]phenyl]ethyl]benzamide;
35 N-[[4-(1H-imidazol-4-ylmethyl)phenyl]methyl]benzamide;
4-chloro-N-[[3-(1H-imidazol-4-ylmethyl)phenyl]methyl]benzamide;
4-chloro-N-[2-[4-(1H-imidazol-4-ylmethyl)phenyl]ethyl]benzamide;
4-chloro-N-[[4-[2-(1H-imidazol-4-yl)ethyl]phenyl]methyl]benzamide;

- 4-(1H-imidazol-4-ylmethyl)-N-[(4-methoxyphenyl)methyl]benzene-carboximidamide;
- 4-(1H-imidazol-4-ylmethyl)-N-[[4-(trifluoromethyl)phenyl]methyl]benzene-carboximidamide;
- 5 4-(1H-imidazol-4-ylmethyl)-N-(4-pyridinylmethyl)benzenecarboximidamide;
- 4-(1H-imidazol-4-ylmethyl)-N-(2-phenylethyl)benzenecarboximidamide;
- 2-[4-(1H-imidazol-4-yl)ethyl]-N-(2-phenylethyl)benzeneethanimidamide;
- 3-(1H-imidazol-4-ylmethyl)-N-(2-phenylethyl)benzenecarboximidamide;
- 4-(1H-imidazol-4-ylmethyl)-N-(2-phenylethyl)benzeneethanimidamide;
- 10 2-[4-(1H-imidazol-4-yl)ethyl]-N-(2-phenylethyl)benzenecarboximidamide;
- 4-(1H-imidazol-4-ylmethyl)benzenecarboximidamide;
- 3-(1H-imidazol-4-ylmethyl)benzenecarboximidamide;
- 3-[2-(1H-imidazol-4-yl)ethyl]benzenecarboximidamide;
- 4-[2-(1H-imidazol-4-yl)ethyl]benzenecarboximidamide;
- 15 4-(1H-imidazol-4-ylmethyl)benzenemethanamine;
- 2-[4-(1H-imidazol-4-ylmethyl)phenyl]ethyl N-[(4-chlorophenyl)methyl]-N-methylcarbamate;
- 2-[4-[2-(1H-imidazol-4-yl)]ethyl]phenyl]ethyl N-[(4-chlorophenyl)methyl]-N-methylcarbamate;
- 20 2-[4-(1H-imidazol-4-ylmethyl)phenyl]ethyl N-(phenylmethyl)-N-methylcarbamate;
- 2-[3-(1H-imidazol-4-ylmethyl)phenyl]ethyl N-[(4-chlorophenyl)methyl]-N-methylcarbamate;
- 2-[4-[2-(1H-imidazol-4-yl)]ethyl]phenyl]ethyl N-[(4-chlorophenyl)methyl]-
- 25 carbamate;
- 2-[4-(1H-imidazol-4-ylmethyl)phenyl]ethyl N-[(4-chlorophenyl)methyl]-carbamate;
- 2-[4-(1H-imidazol-4-ylmethyl)phenyl]ethyl 4-chlorobenzeneacetate;
- 2-[4-[2-(1H-imidazol-4-yl)ethyl]phenyl]ethyl 4-chlorobenzeneacetate;
- 30 2-[4-(1H-imidazol-4-ylmethyl)phenyl]ethyl benzeneacetate;
- 2-[3-(1H-imidazol-4-ylmethyl)phenyl]ethyl 4-chlorobenzeneacetate;
- N'-[(4-chlorophenyl)methyl]-N-[[4-(1H-imidazol-4-ylmethyl)phenyl]methyl]-N,N'-dimethylurea;
- N'-[(4-chlorophenyl)methyl]-N-[2-[4-[2-(1H-imidazol-4-yl)ethyl]phenyl]ethyl]-N,N'-
- 35 dimethylurea;
- N'-(phenylmethyl)-N-[[4-(1H-imidazol-4-ylmethyl)phenyl]methyl]-N,N'-dimethylurea;

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was dissolved in 0.5N HCl and heated to 50°C for one hour. The mixture was cooled, filtered, and washed with ether. The aqueous layer was concentrated and the residue applied to a flash column (85:15 CH₂Cl₂:MeOH/NH₃). Compound **8** was obtained as a white solid (0.125 g, 44%).

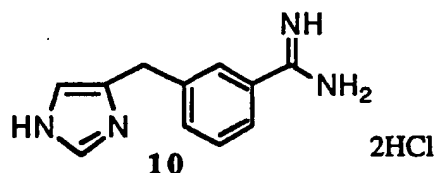
5 Part B.



A solution of **8** (0.12 g, 0.56 mmol) and Raney-Nickel (about 0.1 g wet) were hydrogenated on a Parr shaker under 4.4 kg.cm.⁻² H₂ pressure (63 psi H₂) at room temperature overnight. The heterogeneous mixture was filtered through
 10 Celite, and the filter cake washed with additional ethanol. The ethanol was removed on the rotary evaporator, and the residue purified by HPLC (RCM 25x10 silica gel column eluted with acetonitrile:water:conc. HCl 1600 mL:400 mL:0.5 mL at 3 mL/min.). Compound **9** (0.123 g, 81%) was obtained as a glass.

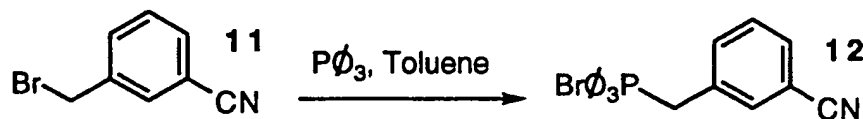
15 Example 4: 3-[(1H-Imidazol-4-yl)methyl]benzene methanimidamide (as dihydrochloride)

In the same manner as that used to prepare compound **9**, compound **10** was prepared.



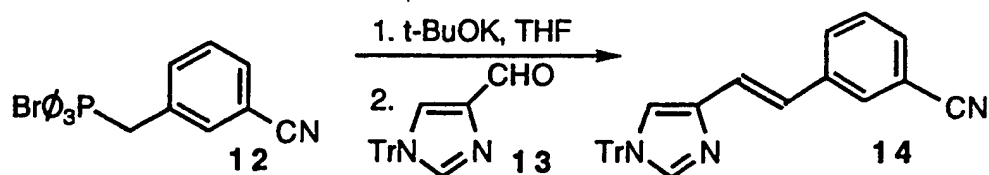
20 Example 5: 3-[(1H-Imidazol-4-yl)ethyl]benzene methanimidamide (as dihydrochloride)

Part A.

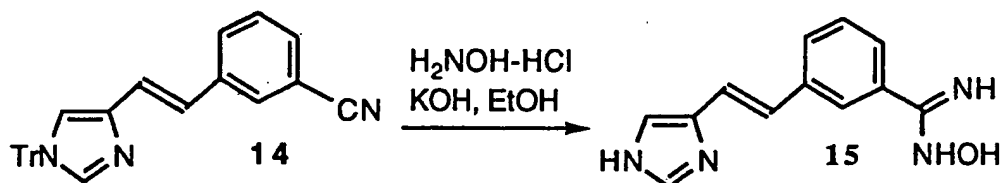


The nitrile **11** (9.8 g, 0.05 mole) and triphenylphosphine (14.4 g, 0.055 mole) were combined in toluene (100 mL) and heated to reflux under a nitrogen
 25 atmosphere for 8 hours. A white precipitate formed. The reaction was cooled, and the solid was collected by filtration and washed with toluene (150 mL), and dried under vacuum. A white solid was obtained (19.7 g, 86%) and used without further purification in the next step.

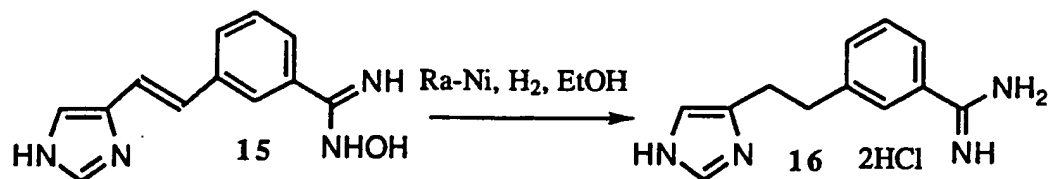
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Part B.

- A solution of potassium t-butoxide in THF (16.3 mL of a 1M solution) was added dropwise to a suspension of the phosphonium salt **12** (7.45 g, 16.3 mmol) in dry THF (45 mL) under a nitrogen atmosphere at room temperature. The orange suspension was stirred for three minutes and a solution of the aldehyde **13** (5 g, 14.8 mmol) [prepared according to Bernabé and Burger; *J. Med. Chem.*, 14 (1971) 883-885] in dry THF (45 mL) was added. After 3.5 hours at room temperature, the reaction was diluted with ether and filtered through Celite. The Celite was washed with additional ether. The organic layer was dried (MgSO₄) and concentrated to give a solid that was purified on a flash column (SiO₂, 1:1 hexane:ethyl acetate) to give 5.03 g (78%) of **14** as a white solid.

Part C.

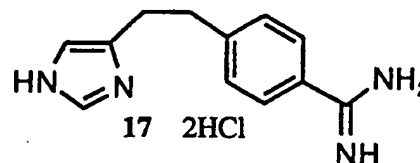
- Hydroxylamine hydrochloride (8 g, 115 mmol) and potassium hydroxide (6.8 g, 121 mmol) were combined in ethanol (100 mL) and heated to 50°C for 10 minutes. A solution of **14** (5.03 g, 11.5 mmol) in ethanol (100 mL) was added and the reaction heated to reflux for 2 hours. It was cooled, filtered and concentrated. The solid that was obtained was dissolved in 1N HCl (80 mL) and heated to 60°C. After 1.5 hours the reaction mixture was filtered and the aqueous layer was washed with ether and concentrated. The residue was dissolved in methanol/NH₃ and stirred for twenty minutes. The solvent was removed and the residue dissolved in ethyl acetate and methylene chloride (80:20) and washed with water. The aqueous layer was extracted again and the combined organic layers were dried (MgSO₄), filtered, and concentrated to give 2.5 g (94 %) of **15** as a white solid.

Part D.

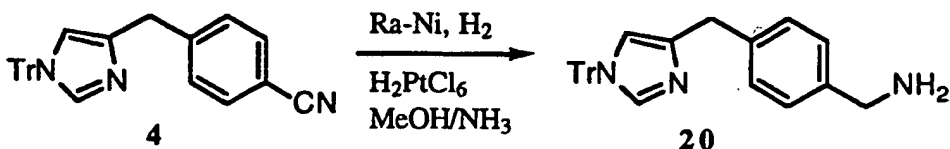
Raney nickel (about 0.5 g wet) and compound **15** (0.46 g, 2 mmol) in ethanol (50 mL) were combined in a Parr bottle and hydrogenated under 4.2 kg.cm.⁻² H₂ pressure (60 psi H₂) 60 psi H₂. After 20 hours, the mixture was filtered and the residue was washed with additional ethanol. Upon concentration, an amber gum was obtained which was purified by HPLC (RCM 25x10, SiO₂, acetonitrile:water:conc. HCl 1600 mL:400:0.5, 3 mL/min, 254 nm). Compound **16** was obtained as a glass (0.31 g, 54%).

10 Example 6 4-[(1H-imidazol-4-yl)ethyl]benzene methanimidamide (as dihydrochloride)

In a manner similar to that used to prepare compound **16**, compound **17** was prepared.

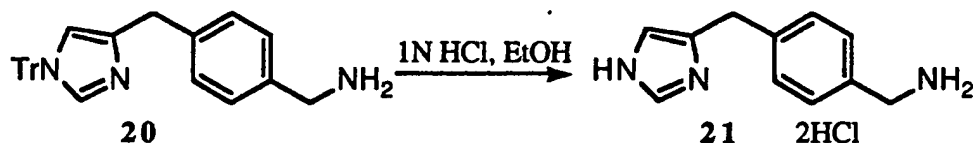


15 Example 7: 4-[(1H-imidazol-4-yl)methyl]benzenemethanamine (as dihydrochloride)

Part A.

Compound **4** (1.53 g, 3.6 mmol) was combined with Raney-Nickel (about 1 g), methanol saturated with ammonia (50 mL), and chloroplatinic acid (0.8 mL of a solution of 1.0 g of the acid in 10 mL of water) in a Parr bottle and shaken under 4.2 kg.cm.⁻² H₂ pressure (60 psi H₂) for 24 hours. The reaction was filtered through Celite and concentrated on the rotary evaporator. The crude material was purified on a flash column (200 g SiO₂; 95:5 CH₂Cl₂:MeOH/NH₃) to give 1.31 g (85%) of **20** as a white solid.

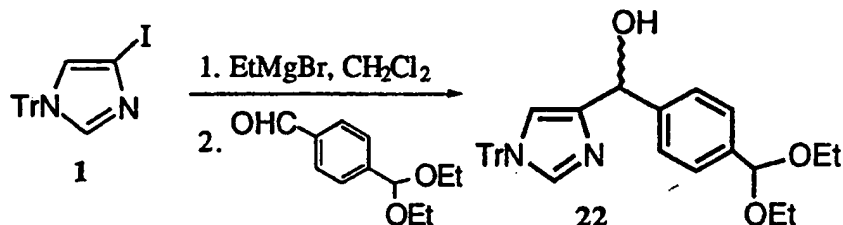
Part B.



To a solution of **20** (1.31 g, 3.1 mmol) in absolute ethanol (30 mL) was added 1N HCl (20 mL) and the heterogeneous mixture heated to 70°C for 2 hours. The reaction was cooled, filtered, and concentrated. Water (50 mL) was added and the solution washed with ether. The aqueous layer was concentrated to give a white solid (0.8 g, 99%).

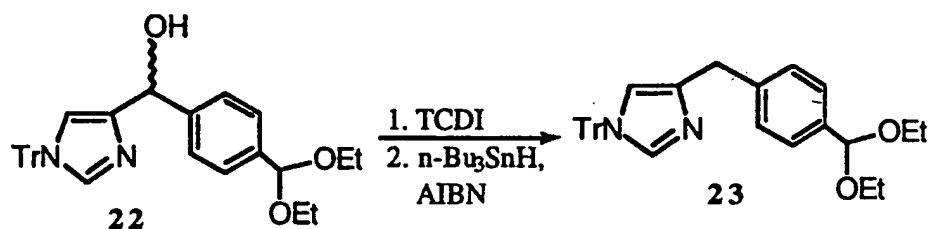
Example 8: N-[(4-Chlorophenyl)methyl]-4-[(1H-imidazol-4-yl)methyl]benzene propanimidamide (as dihydrochloride)

10 Part A.



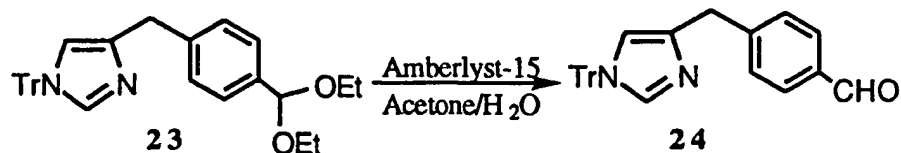
In an analogous manner to that described in Example 1 Part A, compound **22** was obtained in 81% yield by the reaction of the Grignard reagent derived from **1** and terephthalaldehyde mono-(diethylacetal).

15 **Part B.**



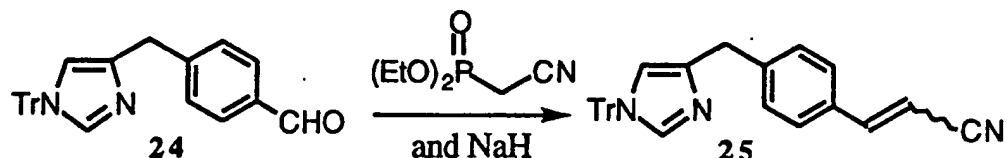
In a manner similar to that described in Example 1 Part B above, compound **23** was derived from compound **22** in 36% overall yield.

Part C.

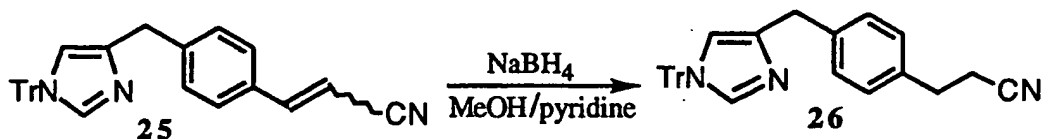


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To a solution of **23** (1.37 g, 2.73 mmol) in acetone (15 mL) was added Amberlyst-15 resin (0.15 g) and water (0.2 mL). The reaction was stirred overnight at room temperature and filtered, and the resin washed with additional acetone (25 mL). After drying (MgSO₄) and concentration, a white solid was
5 obtained (1.03 g, 88%) that was used without further purification.

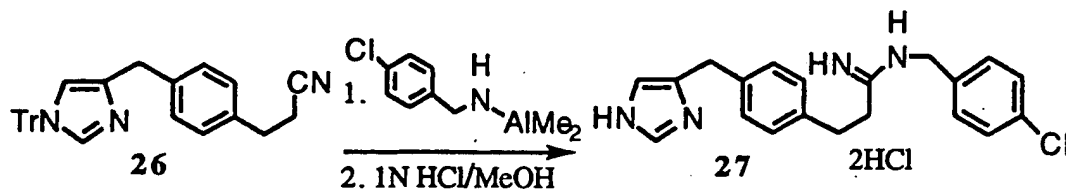
Part D.

Neat diethyl cyanomethylphosphonate (2.6 mmol, 0.46 g) was added dropwise over 10 min to a pentane-washed suspension of NaH (0.104 g of a
10 60% suspension in mineral oil, 2.6 mmol) in THF (30 mL) under argon at 0°C. After 45 min., aldehyde **24** (0.86 g, 2 mmol) in THF (30 mL) was added and the reaction stirred for 4 hours. The reaction was poured into water and extracted with chloroform (3 x 75 mL). The combined organic layers were washed with 12% NaOH, dried (MgSO₄), and concentrated. The crude olefins **25** were
15 purified on a flash column (150 g SiO₂; 90:10 ether:hexane) to give 0.63 g of a 7.5:1 *trans*:*cis* mixture of olefins (70%).

Part E.

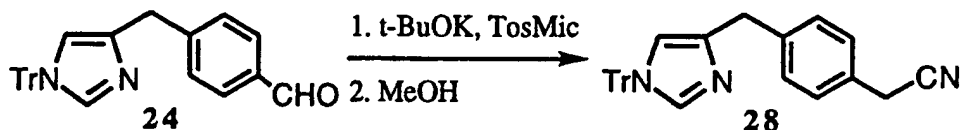
To a solution of **25** (0.43 g, 0.95 mmol) in methanol (0.5 mL) and pyridine
20 (1.5 mL) was added NaBH₄ (0.04 g, 1.05 mmol) portionwise. The reaction was heated to 120°C for 36 hours, cooled and poured into saturated aqueous NH₄Cl. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried with MgSO₄. Filtration and concentration on the rotary evaporator gave a thick oil which was purified on a flash column (75 g SiO₂;
25 ether) to give 0.3 g (70%) of **26**.

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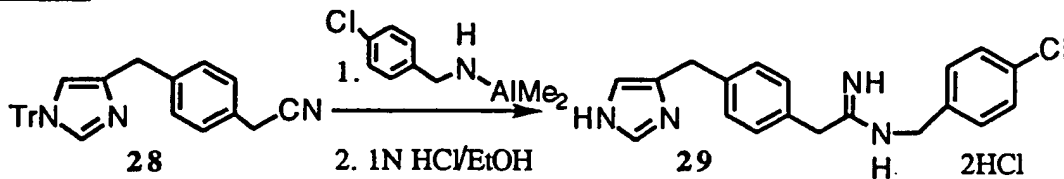
Part E.

In an analogous manner to that described in Example 1 parts C and D above, compound 26 was transformed into compound 27 (36% overall yield).

5 Example 9: N-[(4-Chlorophenyl)methyl]-4-[(1H-imidazol-4-yl)methyl]benzene ethanimidamide (as dihydrochloride)

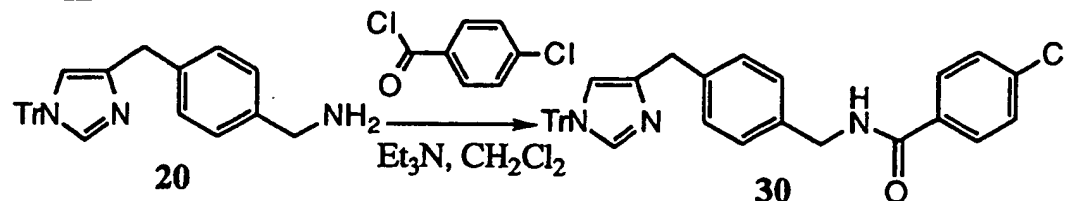
Part A.

To a solution of t-BuOK in THF (6.5 mL of a 1M solution) at -40°C was added a solution of TosMic (tosylmethylisocyanide) (0.66 g, 3.4 mmol) in THF (5 mL) followed by the aldehyde 24 (1.31 g, 3.1 mmol) in THF (5 mL). After 1 hour at this temperature, MeOH (10 mL) was added and the reaction heated to reflux for 20 min. It was then cooled to room temperature and the solvent removed under a stream of nitrogen. The residue was dissolved in CH₂Cl₂ and washed with water/acetic acid (10 mL/0.4 mL). The aqueous layer was extracted with CH₂Cl₂, and the combined organic layers were washed with aqueous NaHCO₃ and dried (MgSO₄). The residue obtained upon filtration and evaporation was purified on a flash column (85:15 hexane:isopropanol) to give 0.55 g (40%) of 28.

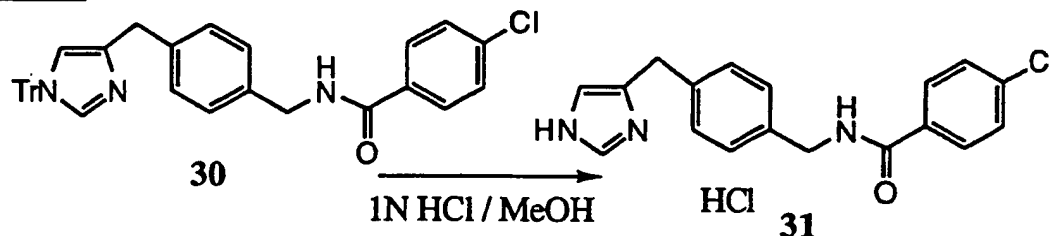
20 Part B.

In a manner analogous to that described in Example 1 Parts C and D above, compound 28 was converted into compound 29.

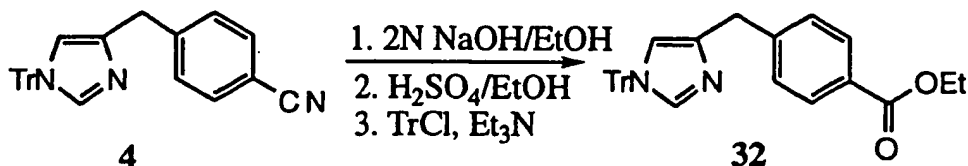
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Example 10: 4-Chloro-N-[[4-[(1H-imidazol-4-ylmethyl)phenyl]methyl]benzamidePart A.

- 5 Distilled Et_3N (0.25 g, 2.5 mmol) was added to a solution of **20** (0.43 g, 1.0 mmol) in dry methylene chloride (10 mL). The solution was cooled in an ice water bath, and 4-chlorobenzoyl chloride (0.19 g, 1.1 mmol) was added slowly (25 min.). After 1 hour, the reaction was poured into ice-water and extracted with methylene chloride (2 x 50 mL). The combined organic layers were washed
- 10 with brine, dried (MgSO_4), and concentrated to give a white solid that was purified by flash column chromatography (95:5 methylene chloride: methanol/ NH_3). Compound **30** was obtained as a white solid (0.55 g, 97%).

Part B.

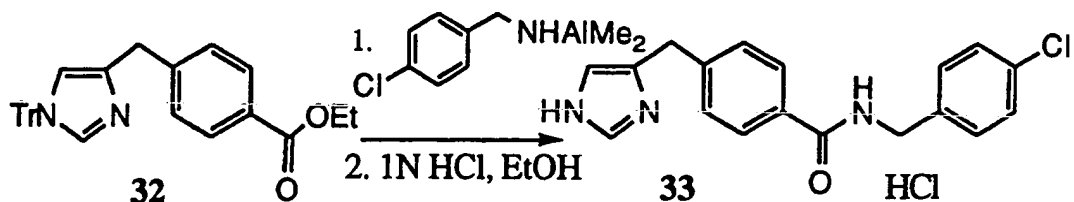
- 15 In a manner analogous to that described in Example 1, Part D, Compound **30** was transformed into compound **31**.

Example 11: N-[(4-Chlorophenyl)methyl]-4-(1H-imidazol-4-ylmethyl)benzamidePart A

- 20 Compound **4** (3 g, 7.1 mmol), 2N NaOH (7.5 mL), and ethanol (35 mL) were heated to reflux for 20 hours. The reaction mixture was cooled to room temperature and concentrated to a paste. Ethanol (50 mL) was added and the mixture concentrated again. This procedure was repeated with toluene.
- 25 Sulfuric acid (3 mL) and ethanol (30 mL) were added to the residue, and the

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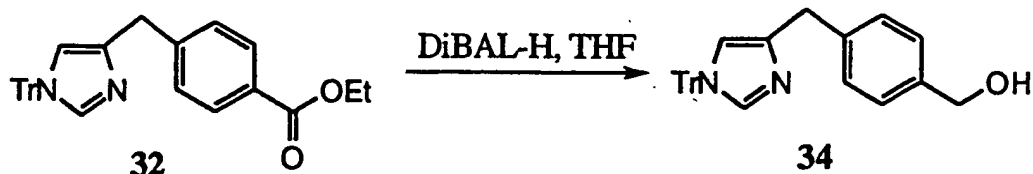
mixture was heated to reflux for 20 hours. The reaction mixture was cooled to room temperature and adjusted to pH 8 with 2N NaOH. Water was added, and the aqueous mixture extracted with methylene chloride (4 x 35 mL). The combined organic layers were dried and concentrated. The crude product was redissolved in dry methylene chloride (60 mL) and triethylamine (1.96 mL), and trityl chloride (2.34 g) were added. After 4 hours, additional methylene chloride (100 mL) was added and the reaction mixture was washed with water and brine. The crude material obtained upon drying and concentration was purified on a flash column (ether) to give **32** as a white solid (1.9 g, 57%).

10 Part B

In a manner analogous to that described in Example 1 Parts C and D above, compound **32** was converted into compound **33**.

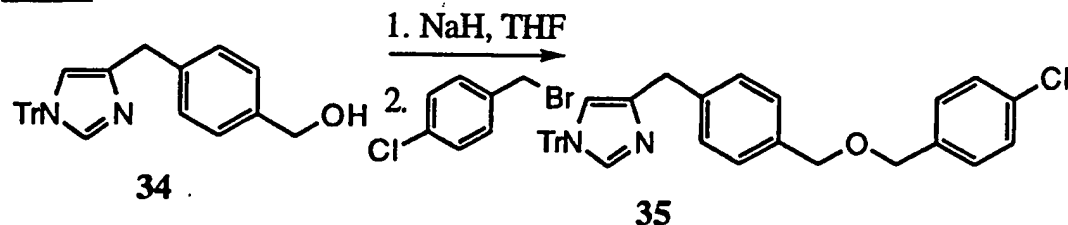
Example 12: 4-[[4-[[4-(4-Chlorophenyl)methoxy]methyl]phenyl]methyl]-1H-imidazole

15

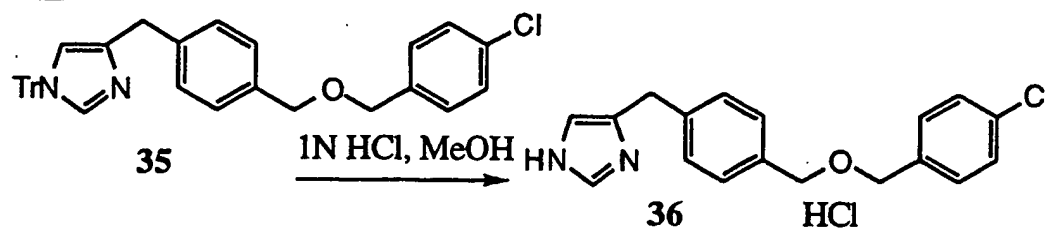
Part A

DiBAL-H was added dropwise over 3 min. to a solution of **32** (1 g, 2.1 mmol) in dry THF (14 mL) at 0°C. After 30 min., the reaction was quenched by the slow addition of 2N NaOH. The reaction mixture was poured into ether (60 mL) and additional 2N NaOH (1.5 mL) and water (1.5 mL) were added. After stirring for 10 min., the turbid mixture was washed with water. The water layer was back-extracted with additional ether (25 mL), and the combined ether layers were dried (MgSO₄). The crude material was purified on a flash column (ether) to give 0.84 g (93%) of **34** as a white solid.

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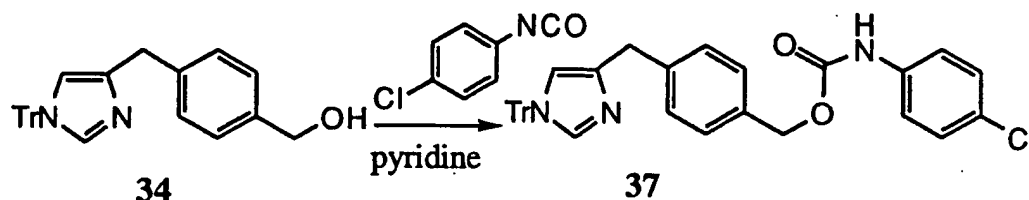
Part B.

- NaH (0.032 g of a 60% dispersion in mineral oil, 0.8 mmol) was added to a solution of **34** (0.26 g, 0.6 mmol) in dry THF (5 mL) at 0°C. The reaction was allowed to warm to room temperature and then stirred for 20 min.; it was then recooled to 0°C, and 4-chlorobenzyl bromide (0.12 g, 0.6 mmol) was added. The reaction was slowly warmed to room temperature and stirred overnight. Additional NaH (0.008 g) and 4-chlorobenzyl bromide (0.041 g) were added and the reaction mixture was stirred an additional 6 hours. The reaction was diluted with ether and washed with water and brine. After drying (MgSO₄), the crude material was purified on a flash column (90:10 ether:hexane) to give **35** as a white solid (0.15 g, 46%).

Part C

- In a manner analogous to that described in Example 1, Part D, compound **35** was transformed into compound **36**.

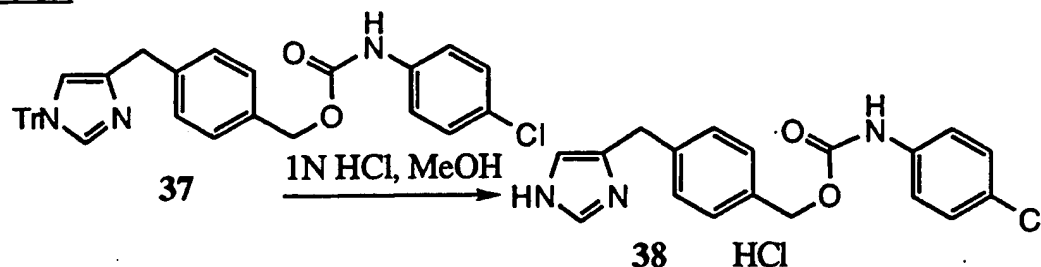
Example 13: [4-(1H-imidazol-4-ylmethyl)phenyl]methyl N-(4-chlorophenyl)carbamate

Part A

- 4-Chlorophenyl isocyanate (0.1 g, 0.66 mmol) was slowly added to a solution of **34** (0.26 g, 0.6 mmol) in dry pyridine (4 mL) at 0°C. When TLC (ether) indicated complete reaction, the pyridine was removed under reduced pressure. The residue was dissolved in methylene chloride (50 mL) and

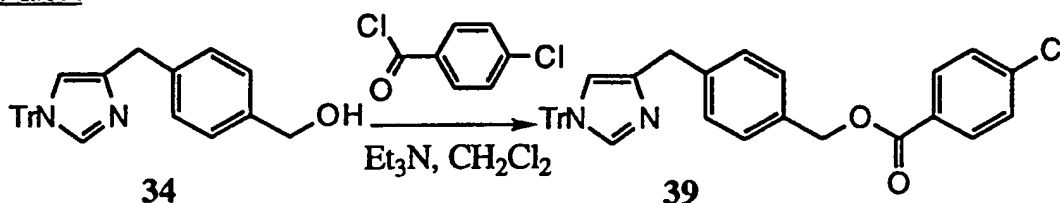
- 36 -

washed with saturated aqueous NaHCO_3 and water and dried (MgSO_4). The residue obtained upon concentrating was purified on a flash column (80:20 ether:hexane) to give 0.15 g (43%) of **37** as a white solid.

Part B

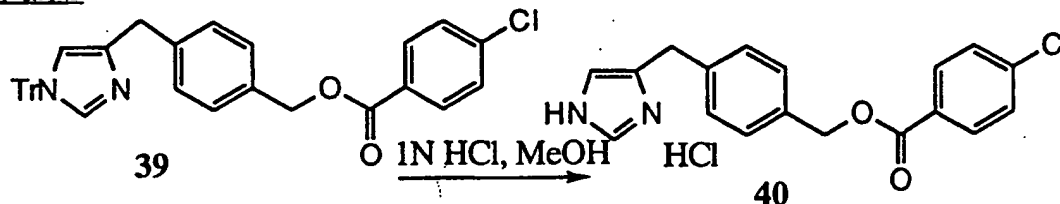
5

In a manner analogous to that described in Example 1, Part D, compound **37** was transformed into compound **38**.

Example 14: [4-(1H-imidazol-4-ylmethyl)phenyl]methyl 4-chlorobenzoylatePart A

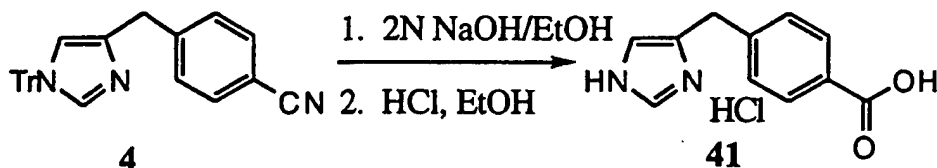
10

4-Chlorobenzoyl chloride (0.12 g, 0.66 mmol) was slowly added over 20 min. to a solution of **34** (0.26 g, 0.6 mmol) and triethylamine (0.15 g, 1.5 mmol) in dry methylene chloride (10 mL) at 0°C. After 30 min., the reaction was diluted with additional methylene chloride (30 mL) and poured into half-saturated NaHCO_3 (20 mL). The organic layer was separated, and the aqueous layer was further extracted with methylene chloride (25 mL). The combined organic layers were dried (MgSO_4) and concentrated to give a foam that was purified on a flash column (80:20 ether:hexane). Compound **39** (0.22 g, 64%) was obtained as a white solid.

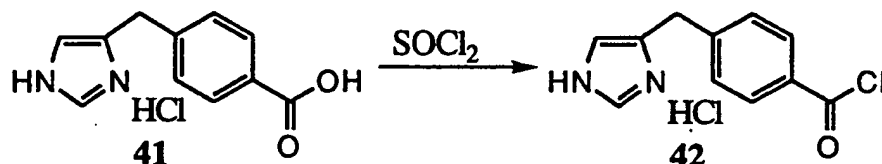
20 Part B

In a manner analogous to that described in Example 1, Part D, compound **39** was transformed into compound **40**.

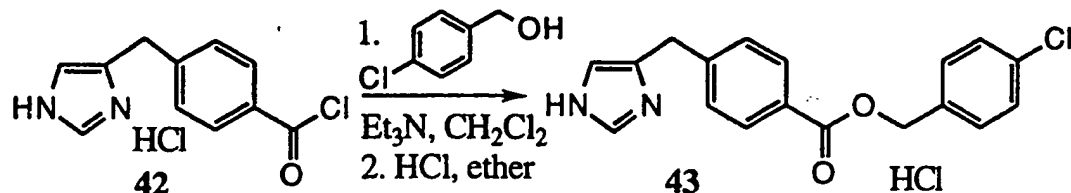
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Example 15: (4-Chlorophenyl)methyl 4-(1H-imidazol-4-ylmethyl)benzoatePart A

- A suspension of 4 (1 g, 2.4 mmol) in ethanol (5 mL) and 2N NaOH (5 mL) was heated to reflux for 20 hours. After cooling, the solvent was removed under reduced pressure and the residue was suspended in 1N HCl (25 mL) and heated to 60°C for 2 hours. The remaining solid was removed by filtration after cooling, and the aqueous layer was concentrated to give a solid. This was used in the next step without purification.

10 Part B

- The residue from Part A was suspended in SOCl₂ (20 mL) and stirred for 20 hours at room temperature. The excess SOCl₂ was removed under reduced pressure and the residue dried by azeotropic removal of toluene. The resulting yellow solid was used directly in the next step without purification.

Part C

- 4-Chlorobenzyl alcohol (0.71 g, 5 mmol) and triethylamine (1.01 g, 10 mmol) were added to a suspension of the acid chloride from Part B in dry methylene chloride (15 mL) at 0°C. The reaction mixture was warmed to room temperature and stirred for 24 hours. Additional methylene chloride (50 mL) was added and the organic layer was washed with saturated aqueous NaHCO₃. The organic layer was separated and dried (MgSO₄). Concentration gave an amber oil that was purified on a flash column (97:3 CH₂Cl₂:MeOH/NH₃). A white solid was obtained (0.36 g, 46% from nitrile 4). This material was dissolved in methylene chloride (10 mL) and 1N HCl in ether (5 mL) was added.

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The solvent was evaporated under a stream of dry argon to give **43** as a white solid (0.4 g, 100%).

Other compounds named herein can be prepared analogously, together with the following compounds:

- 5 N-[(4-chlorophenyl)methyl]-2-fluoro-4-[(1H-imidazol-4-yl)methyl]benzene
methanimidamide;
 N-[(4-chlorophenyl)methyl]-2-chloro-4-[(1H-imidazol-4-yl)methyl]benzene
ethanimidamide;
 N-[(4-chlorophenyl)methyl]-3-methyl-4-[(1H-imidazol-4-yl)methyl]benzene
10 methanimidamide;
 N-[(4-chlorophenyl)methyl]-2-(1-propenyl)-4-[(1H-imidazol-4-yl)methyl]benzene ethanimidamide;
 N-[(4-chlorophenyl)methyl]-3-trifluoromethyl-4-[(1H-imidazol-4-yl)methyl]benzene methanimidamide;
15 N-[(4-chlorophenyl)methyl]-2-(1-propynyl)-4-[(1H-imidazol-4-yl)methyl]benzene ethanimidamide;
 N-[(4-chlorophenyl)methyl]-3-methoxy-4-[(1H-imidazol-4-yl)methyl]benzene methanimidamide;
 N-[(4-chlorophenyl)methyl]-2-dimethylamino-4-[(1H-imidazol-4-yl)methyl]benzene ethanimidamide; and
20 N-[(4-chlorophenyl)methyl]-3-methylthio-4-[(1H-imidazol-4-yl)methyl]benzene methanimidamide.

TABLE 2: MASS SPECTRAL DATA FOR COMPOUNDS OF THE EXAMPLES:

Compound Number	Mass Spectrum	Compound Number	Mass Spectrum
6	Calc: 325.1220 Found: 325.1231	21	Calc: 187.1109 Found: 187.1122
6a	Calc: 320.1637 Found: 320.1620	27	Calc: 352.1455 Found: 352.1476
6b	Calc: 358.1404 Found: 358.1411	29	Calc: 338.1298 Found: 338.1314
6c	Calc: 291.1484 Found: 291.1500	31	Calc: 326.1060 Found: 326.1059
6d	Calc: 304.1688 Found: 304.1702	33	Calc: 326.1060 Found: 326.1059
9	Calc: 200.1062 Found: 200.1074	36	Calc: 313.1108 Found: 313.1108
10	Calc: 201.1140 Found: 201.1152	38	Calc: 342.1009 Found: 342.0998
16	Calc: 215.1297 Found: 215.1305	40	Calc: 327.0900 Found: 327.0891
17	Calc: 215.1297 Found: 215.1292	43	Calc: 327.0900 Found: 327.0897

H₃ Receptor Binding:**H₃ Receptor Binding Assay**

- The source of the H₃ receptors in this experiment was guinea pig brain.
- 5 The animals weighed 400-600 g. The brain tissue was homogenized using a Polytron in a solution of 50 mM Tris, pH 7.5. The final concentration of tissue in the homogenization buffer was 10% w/v. The homogenates were centrifuged at 1,000 x g for 10 min. in order to remove clumps of tissue and debris. The resulting supernatants were then centrifuged at 50,000 x g for 20 min. in order to
- 10 sediment the membranes, which were next washed three times in homogenization buffer (50,000 x g for 20 min. each). The membranes were frozen and stored at -70°C until needed.

- All compounds to be tested were dissolved in DMSO and then diluted into the binding buffer (50 mM Tris, pH 7.5) such that the final concentration was
- 15 2 µg/mL with 0.1% DMSO. Membranes were then added (400 µg of protein) to the reaction tubes. The reaction was started by the addition of 3 nM [³H]R-α-methylhistamine (8.8 Ci/mmol) or 3 nM [³H]N^α-methylhistamine (80 Ci/mmol)

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and continued under incubation at 30°C for 30 min. Bound ligand was separated from unbound ligand by filtration, and the amount of radioactive ligand bound to the membranes was quantitated by liquid scintillation spectrometry. All incubations were performed in duplicate and the standard error was always less than 10%. Compounds that inhibited more than 70% of the specific binding of radioactive ligand to the receptor were serially diluted to determine a K_i (μ M). The results are given in Table 3 and Table 4.

Table 3: K_i (μ M) values

Compound Number	K_i (μ M)	Compound Number	K_i (μ M)	Compound Number	K_i (μ M)
6	0.0140	9	0.038	21	0.078
6a	0.56	10	0.31	27	0.18
6b	0.14	16	0.22	29	0.0072
6d	0.45	17	0.17	38	0.024

Table 4: Inhibition of binding of radioactive ligand

Compound Number	Inhibition (%) at 2 μ g/ml	Compound Number	Inhibition (%) at 2 μ g/ml
6c	48	36	6 - 87
30	61	40	10
33	61	43	16 - 78

10 From these test results and the background knowledge about the compounds described in the references in the section "Background of the Invention", it is to be expected that the compounds of the invention would be useful in treating inflammation, allergy, diseases of the GI-tract, cardiovascular disease, or disturbances of the central nervous system.

15 Pharmaceutically acceptable inert carriers used for preparing pharmaceutical compositions from the compounds of Formula I and their salts can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may comprise from about 5 to about 70 percent active ingredient.

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Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

5 Liquid form preparations include solutions, suspensions and emulsions, for example water or water-propylene glycol solutions for parenteral injection. Liquid form preparations may also include solutions for intranasal administration.

10 Also included are solid form preparations which are intended for conversion, shortly before use, into liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

15 For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into conveniently sized molds, and allowed to cool and thereby solidify.

20 Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose. The quantity of active compound in a unit dose of preparation
25 may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg to 500 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. The determination of the proper dosage for a particular condition is within the skill of
30 the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

35 The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgement of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being

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treated. A typical recommended dosage regimen is oral administration of from 1 mg to 2000 mg/day, preferably 10 to 1000 mg/day, in one to four divided doses to achieve relief of the symptoms. The compounds are non-toxic when administered at therapeutic doses.

- 5 The following are examples of pharmaceutical dosage forms which contain a compound of the invention. As used therein, the term "active compound" is used to designate one of the compounds of the formula I or salt thereof, especially compounds 6 and 29 herein (as free base), namely N-[(4-chlorophenyl)methyl]-4-[(1H-imidazol-4-yl)methyl]benzene methanimidamide and N-[(4-chlorophenyl)methyl]-4-[(1H-imidazol-4-yl)methyl]benzene
- 10 ethanimidamide, or the dihydrochloride thereof, but any other compound of the formula I or salt thereof can be substituted therefor:

Pharmaceutical Dosage Form Examples

EXAMPLE A

Tablets

<u>No.</u>	<u>Ingredients</u>	<u>mg/tablet</u>	<u>mg/tablet</u>
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	<u>3</u>	<u>7</u>
	Total	300	700

Method of Manufacture

- 15 Mix Items No. 1 and 2 in a suitable mixer for 10 to 15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add
- 20 Item No. 5 and mix for 1 to 3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

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EXAMPLE BCapsules

<u>No.</u>	<u>Ingredient</u>	<u>mg/capsule</u>	<u>mg/capsule</u>
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	<u>4</u>	<u>7</u>
	Total	250	700

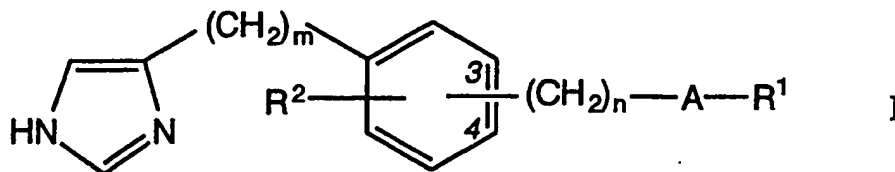
Method of Manufacture

- Mix Items No. 1, 2 and 3 in a suitable blender for 10 to 15 minutes. Add
- 5 Item No. 4 and mix for 1 to 3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

- While a number of embodiments of this invention are described herein, it is apparent that the embodiments can be altered to provide other embodiments that utilize the compositions and processes of this invention. Therefore, it will be
- 10 appreciated that the scope of this invention includes alternative embodiments and variations which are defined in the foregoing Specification and by the Claims appended hereto; and the invention is not to be limited to the specific embodiments that have been presented herein by way of example.

CLAIMS:

1. A compound of the formula

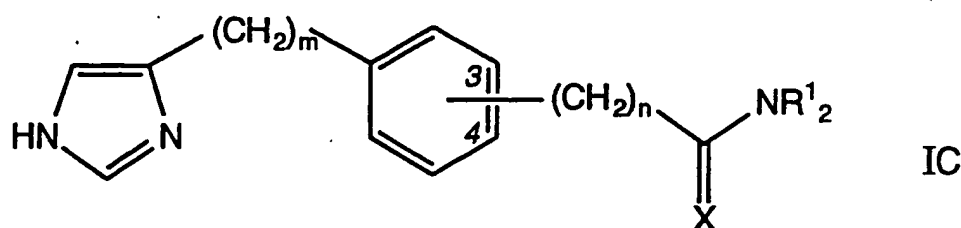


wherein:

- 5 A is selected from $-\text{O}-\text{CO}-\text{NR}^1-$, $-\text{O}-\text{CO}-$, $-\text{NR}^1-\text{CO}-\text{NR}^1-$, $-\text{NR}^1-\text{CO}-$, $-\text{NR}^1-$, $-\text{O}-$, $-\text{CO}-\text{NR}^1-$, $-\text{CO}-\text{O}-$, and $-\text{C}(\text{:NR}^1)-\text{NR}^1-$;
- the groups R^1 , which may be the same or different when there are two or three such groups in the molecule of formula I, are selected from hydrogen, and lower alkyl, aryl, cycloalkyl, heterocyclic and heterocyclyl-alkyl groups, and groups of
- 10 the formula $-(\text{CH}_2)_y-\text{G}$, where G is selected from CO_2R^3 , COR^3 , CONR^3R^4 , OR^3 , SR^3 , NR^3R^4 , heteroaryl and phenyl, which phenyl is optionally substituted by halogen, lower alkoxy or polyhaloloweralkyl, and y is an integer from 1 to 3;
- R^2 is selected from hydrogen and halogen atoms, and alkyl, alkenyl, alkynyl and trifluoromethyl groups, and groups of the formula OR^3 , SR^3 and NR^3R^4 ;
- 15 R^3 and R^4 are independently selected from hydrogen, and lower alkyl and cycloalkyl groups, or R^3 and R^4 together with the intervening nitrogen atom can form a saturated ring containing 4 to 6 carbon atoms that can be substituted with one or two lower alkyl groups;
- with the proviso that, when y is 1 and G is OR^3 , SR^3 or NR^3R^4 , then neither R^3
- 20 nor R^4 is hydrogen;
- the group $-(\text{CH}_2)_n-\text{A}-\text{R}^1$ is at the 3- or 4-position, and the group R^2 is at any free position;
- m is an integer from 1 to 3;
- and n is 0 or an integer from 1 to 3;
- 25 or a pharmaceutically acceptable acid addition salt thereof;
- or a pharmaceutically acceptable salt thereof with a base when G is CO_2H ;
- including a tautomeric form thereof.

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2. A compound of claim 1 having the formula



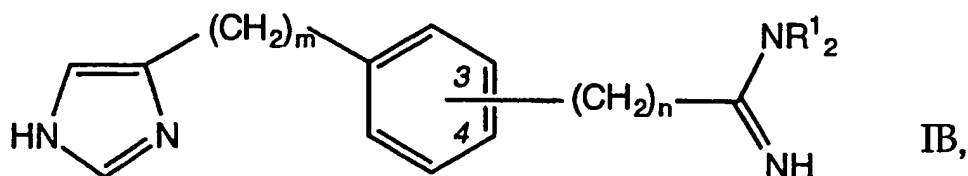
wherein:

X is H₂ or NH;

- 5 the groups R¹, which may be the same or different when there are two or three such groups in the molecule of formula I, are selected from hydrogen, and lower alkyl, aryl, cycloalkyl, and heterocyclic groups, and groups of the formula -(CH₂)_y-G, where G is selected from CO₂R³, COR³, CONR³R⁴, OR³, SR³, NR³R⁴, heteroaryl and phenyl, which phenyl is optionally substituted by
- 10 halogen, lower alkoxy or polyhaloloweralkyl, and y is an integer from 1 to 3;
- m, n, R³ and R⁴ are as defined in claim 1;
- the group (CH₂)_n-CX-NR¹R² is at the 3- or 4-position;
- or a pharmaceutically acceptable acid addition salt thereof;
- or a pharmaceutically acceptable salt thereof with a base when G is CO₂H;
- 15 including a tautomeric form thereof.

3. A compound as claimed in claim 2 wherein m is 1 or 2 and n is 0, 1 or 2.

4. A compound as claimed in claim 3 having the formula



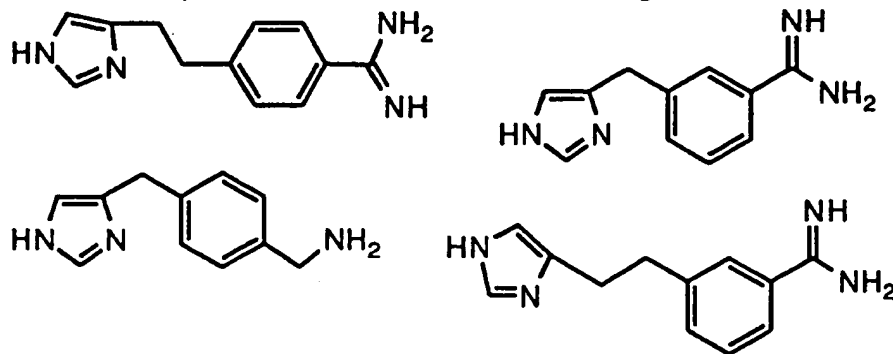
wherein m, n, and R¹ are as defined in claim 1.

- 20 5. A compound of the formula IB defined in claim 4 wherein the side chain -(CH₂)_n-C(=NH)NR¹₂ is at the 4-position.

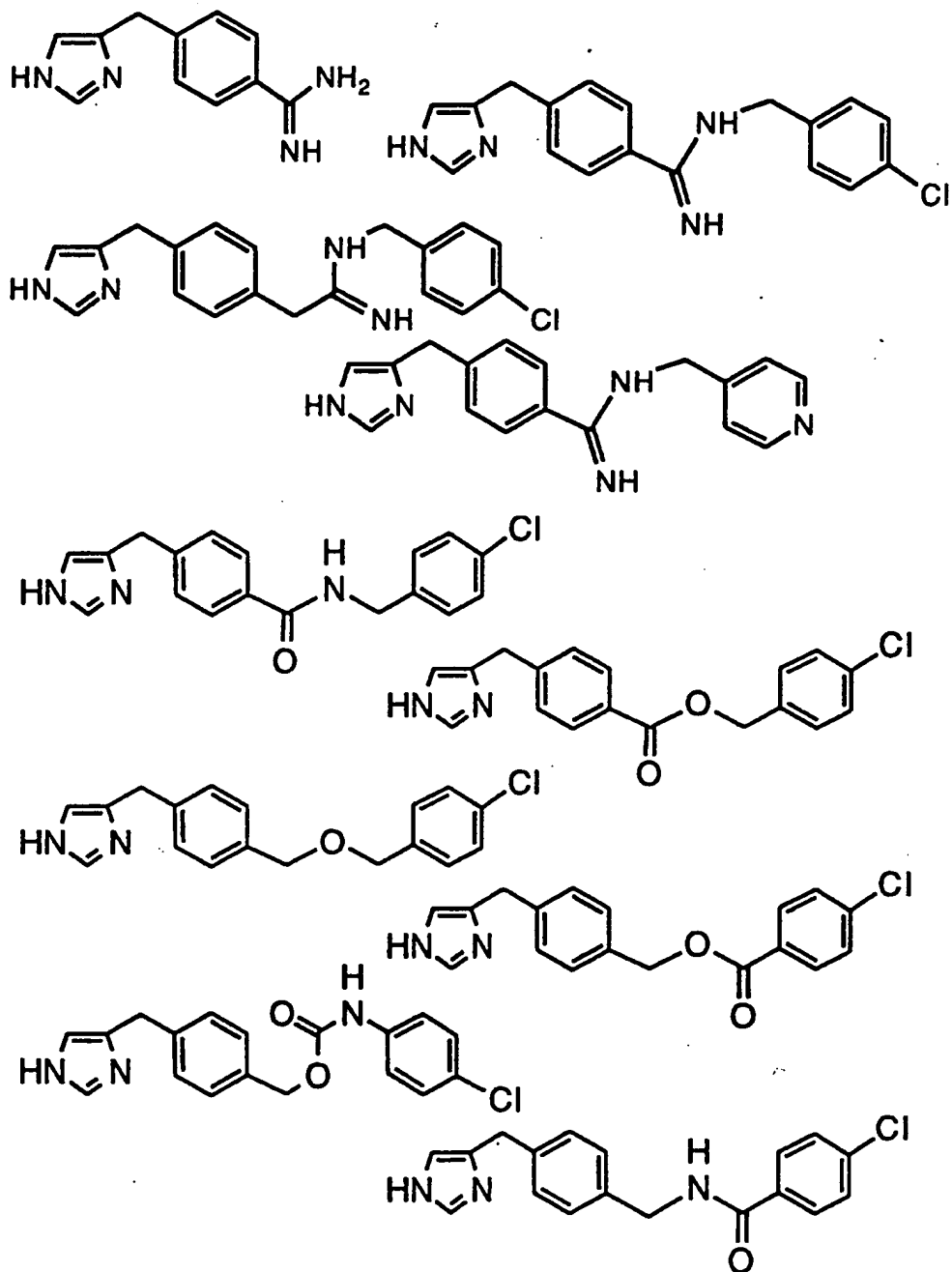
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6. A compound as claimed in claim 5 wherein m is 1 or 2 and n is 0, 1 or 2.
7. A compound as claimed in claim 6 wherein the groups R¹, which may be the same or different, are selected from hydrogen, and aryl groups, and groups of the formula -(CH₂)_y-G, where G is selected from pyridyl and phenyl, which phenyl is optionally substituted by halogen, lower alkoxy or polyhaloloweralkyl, and y is 1 or 2.
8. A compound as claimed in claim 7 wherein one of the groups R¹ is selected from hydrogen, 4-chlorophenylmethyl, 4-methoxyphenylmethyl, 2-phenylethyl, 4-trifluoromethylphenylmethyl and 4-pyridylmethyl, and the other is a hydrogen atom.
9. A compound as claimed in claim 3 wherein A is selected from -CO-O-, -O-CO-NR¹-, and -O-.
10. A compound as claimed in claim 9 wherein the side chain -(CH₂)_n-A-R¹ is at the 4-position, m is 1 or 2 and n is 0, 1 or 2.
11. A compound as claimed in claim 10 wherein the groups R¹, which may be the same or different, are selected from hydrogen, and aryl groups, and groups of the formula -(CH₂)_y-G, where G is selected from pyridyl and phenyl, which phenyl is optionally substituted by halogen, lower alkoxy or polyhaloloweralkyl, and y is 1 or 2.
12. A compound as claimed in claim 11 wherein one of the groups R¹ is selected from hydrogen, 4-chlorophenylmethyl, 4-methoxyphenylmethyl, 2-phenylethyl, 4-trifluoromethylphenylmethyl and 4-pyridylmethyl, and the other is a hydrogen atom.

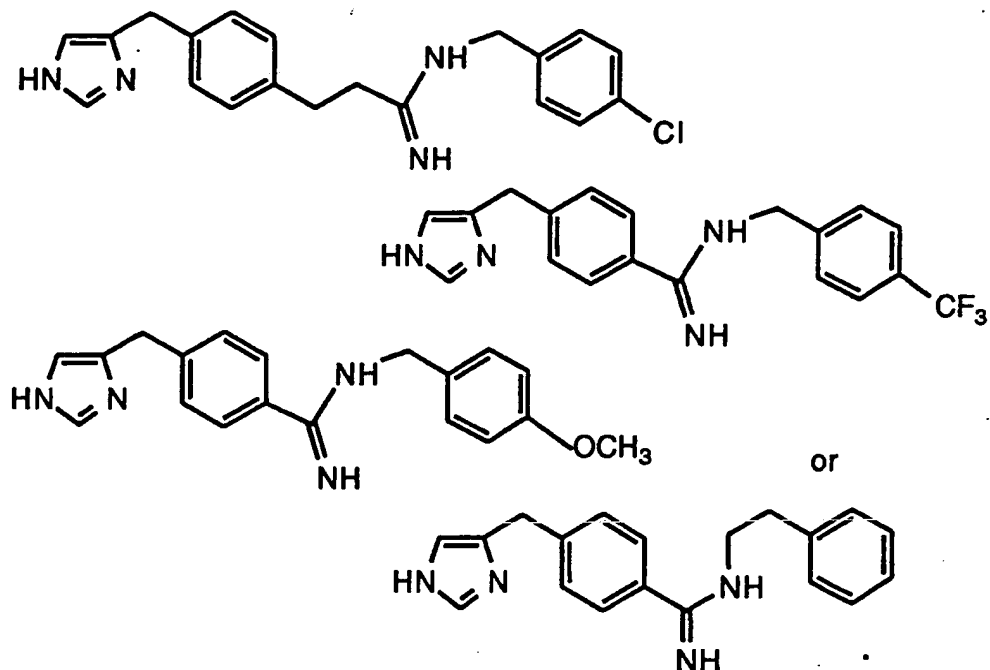
13. A compound as claimed in claim 1 having the formula



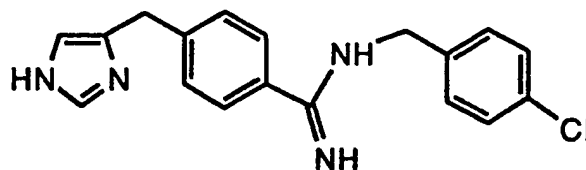
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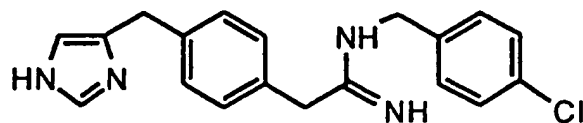


14. A compound of claim 1, having the name N-[(4-chlorophenyl)methyl]-4-[(1H-imidazol-4-yl)methyl]benzene methanimidamide and the structure:



or a pharmaceutically acceptable acid addition salt thereof.

5 15. A compound of claim 1, having the name N-[(4-chlorophenyl)methyl]-4-[(1H-imidazol-4-yl)methyl]benzene ethanimidamide and the structure:



or a pharmaceutically acceptable acid addition salt thereof.

16. The dihydrochloride of the compound of claim 14.

10 17. The dihydrochloride of the compound of claim 15.

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18. A pharmaceutical composition containing as active ingredient a compound of the formula I defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable salt thereof with a base when G is CO₂H, together with a pharmaceutical carrier or excipient.
- 5 19. A method for treating inflammation, which comprises administering to a patient suffering from inflammation an effective amount of a compound or salt as claimed in claim 1.
20. A method for treating allergy, which comprises administering to a patient suffering from allergy an effective amount of a compound or salt as claimed in
10 claim 1.
21. A method for treating diseases of the GI-tract, which comprises administering to a patient suffering from a disease of the GI-tract an effective amount of a compound or salt as claimed in claim 1.
22. A method for treating cardiovascular disease, which comprises
15 administering to a patient suffering from cardiovascular disease an effective amount of a compound or salt as claimed in claim 1.
23. A method for treating disturbances of the central nervous system, which comprises administering to a patient suffering from disturbances of the central nervous system an effective amount of a compound or salt as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/12717

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D233/54 A61K31/415 C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 341 231 (U C B, S.A.) 8 November 1989 see page 15 - page 20; examples 1-2 see page 22, line 27; examples 3-6 ---	1,9
X	EP,A,0 024 829 (FARMOS-YHTYMÄ OY) 11 March 1981 see page 41 - page 42; examples 27,28 --- -/--	1,9,10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- *E* earlier document but published on or after the international filing date
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Date of the actual completion of the international search

7 March 1995

Date of mailing of the international search report

17. 03. 95

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 94/12717

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHEMICAL ABSTRACTS, vol. 118, no. 13, 29 March 1993, Columbus, Ohio, US; abstract no. 124448b, C.J. CARDIN ET AL. 'Synthesis of 3-[4(5)-imidazolylmethyl]-2-methylbenzoic acid, a metabolite of the drug detomidine.' page 800 ;column 2 ; see abstract and Chemical Abstracts, CHEMICAL SUBSTANCE INDEX, vol 118, 1993, pages 1406CS and 1688CS: RN [115664-37-4], 115664-39-6] and [146197-56-0] & J. CHEM. RES., SYNOP., no.12, 1992 page 389</p> <p style="text-align: center;">---</p>	1,9
X	<p>CHEMICAL ABSTRACTS, vol. 112, no. 15, 9 April 1990, Columbus, Ohio, US; abstract no. 139033, N. KIHARA ET AL. 'Preparation of imidazole derivatives as drugs.' page 721 ;column 2 ; see abstract and Chemical Abstracts, CHEMICAL SUBSTANCES, 12th Collective Index, vol. 106-115, 1987-1991, pages 7972CS and 45772CS: RN [125883-66-1] and [78892-56-5] & JP,A,01 242 571 (MITSUI PETROCHEMICAL INDUSTRIES, LTD.) 27 September 1989</p> <p style="text-align: center;">---</p>	1,9,10
X	<p>CHEMICAL ABSTRACTS, vol. 109, no. 25, 19 December 1988, Columbus, Ohio, US; abstract no. 231016v, E. COSSEMENT ET AL. 'Preparation of 4-(substituted benzyl)imidazoles as antiischemic agents.' page 862 ;column 2 ; see abstract and Chemical Abstracts, CHEMICAL SUBSTANCES, 12th Collective Index, vol. 106-115, 1987-1991, page 12424CS: RN [116796-03-3] & EP,A,0 269 599 (U C B, S.A.) 1 June 1988</p> <p style="text-align: center;">---</p>	1,9
X	<p>RECUEIL DES TRAVAUX CHIMIQUES DES PAYS-BAS, vol.95, no.2, February 1976, DEN HAAG NL pages 45 - 49 J. HORA 'The synthesis of bis-endo-2-(hydr oxymethyl)-5-(4-imidazolymethyl)-bicyclo[2 .2.2]octane and the corresponding cyclohexane analogue' see page 46, column 1, compound no. 16</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1,9,10

INTERNATIONAL SEARCH REPORT

Intern. Patent Application No
PCT/US 94/12717

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 84, no. 5, 2 February 1976, Columbus, Ohio, US; abstract no. 30961r, W. SCHUNACK 'Structure-activity relations of histamine analogs. 9. Aminobenzyl- and aminocyclohexylmethylimidazoles.' page 454 ;column 1 ; see abstract and Chemical Abstracts, CHEMICAL SUBSTANCES, 9th Collective Index, vol. 76-85, 1972-1976, page 3264CS: RN [57662-33-6] and [57662-34-7] & ARCH. PHARM., vol.308, no.10, 1975, WEINHEIM, DE pages 755 - 759 ---	1,9
A	WO,A,93 14070 (INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICAL) 22 July 1993 see page 104 - page 107; claim 1 see page 1, line 15 - line 22 ---	1-23
P,X	JOURNAL OF HETEROCYCLIC CHEMISTRY, vol.30, no.6, December 1993, PROVO US pages 1645 - 1651 I. STOILOV ET AL. 'Synthesis of Detomidine and Medetomidine Metabolites: 1,2,3-Trisubstituted Arenes with 4'(5')-Imidazolylmethyl Groups' see page 1646, figure 3, compound no. 15 -----	1,9-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/12717

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0341231	08-11-89	AU-B- 610796	23-05-91
		AU-A- 3373089	02-11-89
		ES-T- 2052969	16-07-94
		JP-A- 1313467	18-12-89
		NO-C- 173331	08-12-93
		PT-B- 90368	31-08-94
		SU-A- 1814647	07-05-93
		US-A- 4923865	08-05-90
EP-A-0024829	11-03-81	AT-T- 7226	15-05-84
		AU-B- 518569	08-10-81
		AU-A- 6107180	12-02-81
		CA-A- 1154780	04-10-83
		JP-C- 1396350	24-08-87
		JP-A- 56032463	01-04-81
		JP-B- 62004387	30-01-87
		SU-A- 997607	15-02-83
		SU-A- 1014472	23-04-83
		US-A- 4443466	17-04-84
JP-A-01242571	27-09-89	NONE	
EP-A-0269599	01-06-88	AU-B- 592733	18-01-90
		AU-A- 8059387	05-05-88
		CA-A- 1301174	19-05-92
		DE-D- 3788507	27-01-94
		DE-T- 3788507	19-05-94
		ES-T- 2060608	01-12-94
		FI-B- 91858	13-05-94
		JP-A- 63132876	04-06-88
		SU-A- 1662349	07-07-91
		SU-A- 1710558	07-02-92
		SU-A- 1635899	15-03-91
		SU-A- 1628857	15-02-91
		US-A- 4814343	21-03-89
WO-A-9314070	22-07-93	FR-A- 2686084	16-07-93
		EP-A- 0597088	18-05-94
		JP-T- 6506003	07-07-94